

AGGTTCGCAGGCGGGCGTGCCTGGAGCGGGGGCCGCGCCGCGCCGAGAGATGTGACTCGGGCCGAAGGC  
CAGCTGGAGCGTCGCGCGTGCAGGGCCGCGGGGGTCAATGTTTCGTGGCATCAGAGAGAAAGATGAGAGC  
TCACCAGGTGCTCACCTTCCTCCTGCTCTTCGTGATCACCTCGGTGGCCTCTGAAAACGCCAGCACATCC  
CGAGGCTGTGGGCTGGACCTCCTCCCTCAGTACGTGTCCCTGTGCGACCTGGACGCCATCTGGGGCATTG  
TGGTGGAGGCGGTGGCCGGGGCGGGCGCCCTGATCACACTGCTCCTGATGCTCATCCTCCTGGTGC GGCT  
GCCCTTCATCAAGGAGAAGGAGAAGAAGAGCCCTGTGGGCCTCCACTTCTGTTCCTCCTGGGGACCCTG  
GGCCTCTTTGGGCTGACGTTTGCTTCATCATCCAGGAGGACGAGACCATCTGCTCTGTCCGCCGCTTCC  
TCTGGGGCGTCTCTTTGCGCTCTGCTTCTCCTGCCTGCTGAGCCAGGCATGGCGCGTGCGGAGGCTGGT  
GCGGCATGGCACGGGGCCCCGCGGGCTGGCAGCTGGTGGGCCTGGCGCTGTGCCTGATGCTGGTGCAAGTC  
ATCATCGCTGTGGAGTGGCTGGTGCTCACCGTGCTGCGTGACACAAGGCCAGCCTGCGCCTACGAGCCCA  
TGGACTTTGTGATGGCCCTCATCTACGACATGGTACTGCTTGTGGTCACCCTGGGGCTGGCCCTCTTCAC  
TCTGTGCGGCAAGTTCAAGAGGTGGAAGCTGAACGGGGCCTTCCTCCTCATCACAGCCTTCCTCTCTGTG  
CTCATCTGGGTGGCCTGGATGACCATGTACCTCTTCGGCAATGTCAAGCTGCAGCAGGGGGATGCCTGGA  
ACGACCCACCTTGCCATCACGCTGGCGGCCAGCGCTGGGTCTTCGTTCATCTTCCACGCCATCCCTGA  
GATCCACTGCACCCTTCTGCCAGCCCTGCAGGAGAACACGCCCACTACTTCGACACGTGCGAGCCAGG  
ATGCGGGAGACGGCCTTCGAGGAGGACGTGCAGCTGCCGCGGGCCTATATGGAGAACAAGGCCTTCTCCA  
TGGATGAACACAATGCAGCTCTCCGAACAGCAGGATTTCCCAACGGCAGCTTGGGAAAAAGACCCAGTGG  
CAGCTTGGGGAAAAGACCCAGCGCTCCGTTTAGAAGCAACGTGTATCAGCCAACCTGAGATGGCCGTCGTG  
CTCAACGGTGGGACCATCCCAACTGCTCCGCCAAGTCACACAGGAAGACACCTTTGGTGAAAGACTTTAA  
GTTCCAGAGAATCAGAATTTCTCTTACCGATTTGCCCTCCCTGGCTGTGTCTTTCTTGAGGGAGAAATCGG  
TAACAGTTGCCGAACCAGGCCGCTCACAGCCAGGAAATTTGGAAATCCTAGCCAAGGGGATTTCTGTGTA  
AATGTGAACACTGACGAACCTGAAAAGCTAACACCGACTGCCCGCCCCCTCCCCTGCCACACACACAGACAC  
GTAATACCAGACCAACCTCAATCCCCGAAACTAAAGCAAAGCTAATTGCAAATAGTATTAGGCTCACTG  
GAAAATGTGGCTGGGAAGACTGTTTCATCCTCTGGGGGTAGAACAGAACCAATTCACAGCTGGTGGGCC  
AGACTGGTGTGGTGGAGGTGGGGGGCTCCCACTCTTATCACCTCTCCCAGCAAGTGCTGGACCCAG  
GTAGCCTCTTGAGAGATGACCGTTGCGTTGAGGACAAATGGGGACTTTGCCACCGGCTTGCCTGGTGGTTT  
GCACATTTACAGGGGGGTCAGGAGAGTTAAGGAGGTTGTGGGTGGGATTCCAAGGTGAGGCCCAACTGAAT  
CGTGGGGTGAGCTTTATAGCCAGTAGAGGTGGAGGGACCCTGGCATGTGCCAAAGAAGAGGCCCTCTGGG  
TGATGAAGTGACCATCACATTTGGAAAGTGATCAACCACTGTTTCCTTCTATGGGGCTCTTGCTCTAATGT  
CTATGGTGAGAACACAGGCCCCGCCCCCTTCCCTTGTAGAGCCATAGAAATATTCTGGCTTGGGGCAGCAG  
TCCCTTCTTCCCTTGATCATCTCGCCCTGTTCTTACACTTACGGGTGTATCTCCAAATCCTCTCCCAATT  
TTATTCCCTTATTCAATTTCAAGAGCTCCAATGGGGTCTCCAGCTGAAAGCCCCCTCCGGGAGGCAGGTTGG  
AAGGCAGGCACCACGGCAGGTTTTCCGCGATGATGTACCTAGCAGGGCTTCAGGGGTTCCCACTAGGAT  
GCAGAGATGACCTCTCGCTGCCTACAAGCAGTGACACCTCGGGTCCTTTCCGTTGCTATGGTGAAAATT  
CCTGGATGGAATGGATCACATGAGGGTTTCTTGTTGCTTTTGGAGGGTGTGGGGGATATTTTGTTTTGGT  
TTTTCTGCAGGTTCCATGAAAACAGCCCTTTTCCAAGCCCATTGTTTCTGTTCATGGTTTCCATCTGTCTT  
GAGCAAGTCATTCCTTTGTTATTTAGCATTTTCAACATCTCGGCCATTCAAAGCCCCCATGTTCTCTGCA  
CTGTTTGGCCAGCATAACCTCTAGCATCGATTCAAAGCAGAGTTTTAACCTGACGGCATGGAATGTATAA  
ATGAGGGTGGGTCTTCTGCAGATACTCTAATCACTACATTGCTTTTTCTATAAACTACCCATAAGCCT  
TTAACCTTTAAAGAAAAATGAAAAAGGTTAGTGTTTGGGGGCCGGGGGAGGACTGACCGCTTCATAAGCC  
AGTACGTCTGAGCTGAGTATGTTTCAATAAACCTTTTGATATTTCTCAAAAAAAAAAAAAAAAAAAAAA  
(SEQ ID NO:1)

FIGURE 1A

MFVASERKMRAHQVLTFLLLFVITSVASENASTSRGCGLDLLPQYVSLCDLDAIWGIVVEAVAG  
AGALITLLLMLILLVRLPFIKEKEKKSPVGLHFLFLLGTLGLFGLTFAFIIQEDETICSVRRFL  
WGVLFALCFSCLLSQAWRVRLVRHGTGPAGWQLVGLALCLMLVQVIIAVEWLVLTVLRDTRPA  
CAYEPMDFVMALIYDMVLLVVTGLGLALFTLCGKFKRWKLNGAFLLLITAFLSVLIWVAWMTMYLF  
GNVKLQQGDAWNDPTLAITLAASGWVFVIFHAIPEIHCTLLPALQENTPNYFDTSQPRMRETAF  
EEDVQLPRAYMENKAFSMDEHNAALRTAGFPNGSLGKRPSGSLGKRPSAPFRSNVYQPTEMAVV  
LNGGTIPTAPPSHTGRHLW (SEQ ID NO:2)

**FIGURE 1B**

underlined = deleted in targeting construct

**bold** = sequence flanking Neo insert in targeting construct

AGGTGCGAGGCGGGCGTGGCTGGAGCGGGGGCCGCGGCCGCGCCGAGAGATGTGACTCG  
 GGCCGAAGGCCAGCTGGAGCGTGGGCGCTGCGGGGCCGCGGGGGTGG**AATGTTTCGTGGCA**  
**TCAGAGAGAAAGATGAGAGCTCACCAGGTGCTCACCTTCTCCTGCTCTTCGTGATCACC**  
**TCGGTGGCCTCTGAAAACGCCAGCACATCCCAGGCTGTGGGCTGGACCTCCTCCCTCAG**  
**TACGTGTCCCTGTGCGACCTGGACGCCATCTGGGGCATTGTGGTGGAGGCGGTGGCCGGG**  
**GCGGGCGCCCTGATCACACTGCTCCTGATGCTCATCTCCTGGTGGGCTGCCCTTCATC**  
**AAGGAGAAGGAGAAGAAGAGCCCTGTGGGCTCCACTTTCGTTCCTCCTGGGGACCCTG**  
**GGCCTCTTTGGGCTGACGTTTGCTTCATCATCCAGGAGGACGAGACCATCTGCTCTGTC**  
**CGCCGCTTCTCTGGGGCGTCTCTTTGCGCTCTGCTTCTCCTGCTGCTGAGCCAGGCA**  
**TGGCGCGTGGGAGGCTGGTGGCGCATGGCACGGGGCCCGGGGCTGGCAGCTGGTGGGC**  
**CTGGCGCTGTGCTGATGCTGGTGCAAGTCATCATCGCTGTGGAGTGGCTGGTGGCTCACC**  
**GTGCTGCGTGACACAAGGCCAGCCTGCGCCTACGAGCCCATGGACTTTGTGATGGCCCTC**  
**ATCTACGACATGGTACTGCTTGTGGTCACCCTGGGGCTGGCCCTCTTCACTCTGTGCGGC**  
**AAGTTCAAGAGGTGGAAGCTGAACGGGGCCTTCTCCTCATCACAGCCTTCTCTCTGTG**  
**CTCATCTGGGTGGCCTGGATGACCATGTACCTCTTCGGCAATGTCAAGCTGCAGCAGGGG**  
**GATGCCCTGGAACGACCCACCTTGGCCATCACGCTGGCGGCCAGCGGCTGGGTCTTCGTC**  
**ATCTTCCACGCCATCCCTGAGATCCACTGCACCCTTCTGCCAGCCCTGCAGGAGAACAG**  
**CCCACTACTTTCGACACGTCGCAGCCCAGGATGCGGGAGACGGCCTTCGAGGAGGACGTG**  
**CAGCTGCCCGGGCCTATATGGAGAACAAGGCCTTCTCCATGGATGAACACAATGCAGCT**  
**CTCCGAACAGCAGGATTTCCTAACGGCAGCTTGGGAAAAAGACCCAGTGGCAGCTTGGGG**  
**AAAAGACCCAGCGCTCCGTTTAGAAGCAACGTGTATCAGCCAACTGAGATGGCCGCTCGTG**  
**CTCAACGGTGGGACCATCCCACTGCTCCGCCAAGTCACACAGGAAGACACCTTTGGTGA**  
**AAGACTTTAAGTTCCAGAGAATCAGAATTTCTCTTACCGATTTGCCCTCCCTGGCTGTGTC**  
**TTTCTTGAGGGAGAAATCGGTACAGTTGCCGAACAGGCCGCTCACAGCCAGGAAATTT**  
**TGGAAATCCTAGCCAAGGGGATTTCTGTAAATGTGAACACTGACGAACTGAAAAGCTAA**  
**CACCGACTGCCCGCCCCCTCCCTGCCACACACAGACACGTAATACCAGACCAACCTCA**  
**ATCCCCGCAAACTAAAGCAAAAGCTAATTGCAAAATAGTATTAGGCTCACTGGAAAATGTGG**  
**CTGGGAAGACTGTTTCATCTCTGGGGGTAGAACAGAACCAAAATTCACAGCTGGTGGGCC**  
**AGACTGGTGTGTTGGTGGAGGTGGGGGGCTCCCACTTATCACCTCTCCCCAGCAAGTGC**  
**TGGACCCAGGTAGCCTCTTGGAGATGACCGTTGCGTTGAGGACAAATGGGGACTTTGCC**  
**ACCGGCTTGCTGGTGGTGGTTCACATTTACGGGGGGTCAGGAGAGTTAAGGAGGTTGTGG**  
**GTGGGATTCCAAGGTGAGGCCCACTGAATCGTGGGGTGAGCTTTATAGCCAGTAGAGGT**  
**GGAGGGACCCTGGCATGTGCCAAAGAAGAGGCCCTCTGGGTGATGAAGTGACCATCACAT**  
**TTGGAAAGTGATCAACCACTGTTCTTCTATGGGGCTCTTGCTCTAATGTCTATGGTGAG**  
**AACACAGGCCCCGCCCCCTCCCTTGTAGAGCCATAGAAATATTCTGGCTTGGGGCAGCAG**  
**TCCCTTCTTCCCTTGATCATCTCGCCCTGTTCTTACACTTACGGGTGTATCTCCAAATCC**  
**TCTCCCAATTTTATTCCCTTATTCAATTTCAAGAGCTCCAATGGGGTCTCCAGCTGAAAGC**  
**CCCTCCGGGAGGCAGGTTGGAAGGCAGGCACCACGGCAGGTTTTCCGCGATGATGTCACC**  
**TAGCAGGGCTTCAGGGTTCCCACTAGGATGCAGAGATGACCTCTCGCTGCCTCACAAGC**  
**AGTGACACCTCGGGTCCCTTCCGTTGCTATGGTGAAAATTCCTGGATGGAATGGATCACA**  
**TGAGGGTTTCTTGTGCTTTTGGAGGGTGTGGGGGATATTTTGTTTTGGTTTCTGTCAG**  
**GTTCCATGAAAACAGCCCTTTTCCAAGCCATTGTTTCTGTCATGGTTTCCATCTGTCCT**  
**GAGCAAGTCATTCCTTTGTTATTAGCATTTTCAACATCTCGGCCATTCAAAGCCCCCAT**  
**GTTCTCTGCACTGTTTGGCCAGCATAACCTCTAGCATCGATTCAAAGCAGAGTTTAAACC**  
**TGACGGCATGGAATGTATAAATGAGGGTGGGTCTTCTGCAGATACTCTAATCACTACAT**  
**TGCTTTTCTATAAACTACCCATAAGCCTTTAACCTTTAAAGAAAAATGAAAAAGGTTA**  
**GTGTTTGGGGGCCGGGGAGGACTGACCGCTTCATAAGCCAGTACGCTGAGCTGAGTAT**  
**GTTTCAATAAACCTTTTGATATTCTCAAAAAAAAAAAAAAAAAAAAAA**

FIGURE 2A

Gene Sequence  
Structure \*

526 bp

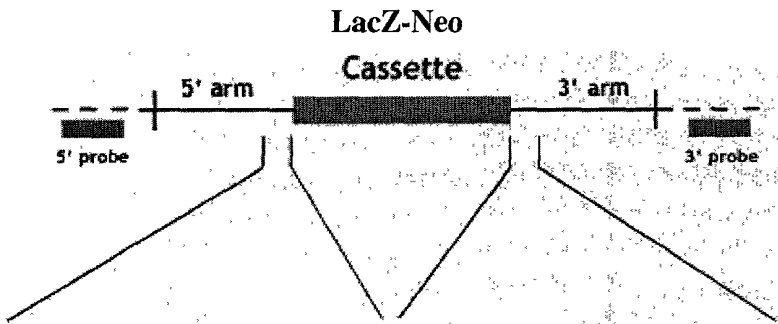
Sequence Deleted

594 bp

Size of full-length  
cDNA: 2870 bp

Targeting Vector\*  
(genomic sequence)

Arm Length:  
5': 4.2 kb  
3': 0.7 kb



<b>5'&gt;</b> TGATGCTCATTCTCCTAGTGA GACTACCCTTCATCAAGGACAAGG AAAGGAAGCGCCTGTGTGCCTCC ATTTCTCTTCCTGCTGGGGACCC TGGGCCCTCTTTGGCCTGACGTTTG CCTTCATCATCCAGATGGACGAGA CAATCTGCTCCATCCGACGCTTCC TCTGGGGTGTCTCTTCGCGCTCT GCTTTTCCGCT<3' (SEQ ID NO:3)	<b>5'&gt;</b> GTGAGCCTGGCACTGTGCCTG ATGCTGGTGCAGGTCATCATTGCC ACTGAGTGGCTGGTGTGACTGTG CTGCGTGACACGAAGCCAGCCTGC GCCTACGAGCCCATGGATTTTGTG ATGGCGCTCATCTACGACATGGTG CTGCTGGCCATCACCTGGCCCAG TCCCTCTTCACGCTGTGTGGCAAG TTCAAACGGTG<3' (SEQ ID NO:4)
--	--

———— Targeting Vector  
- - - - Endogenous Locus

\* Not drawn to scale

FIGURE 2B

## Hot Plate Test

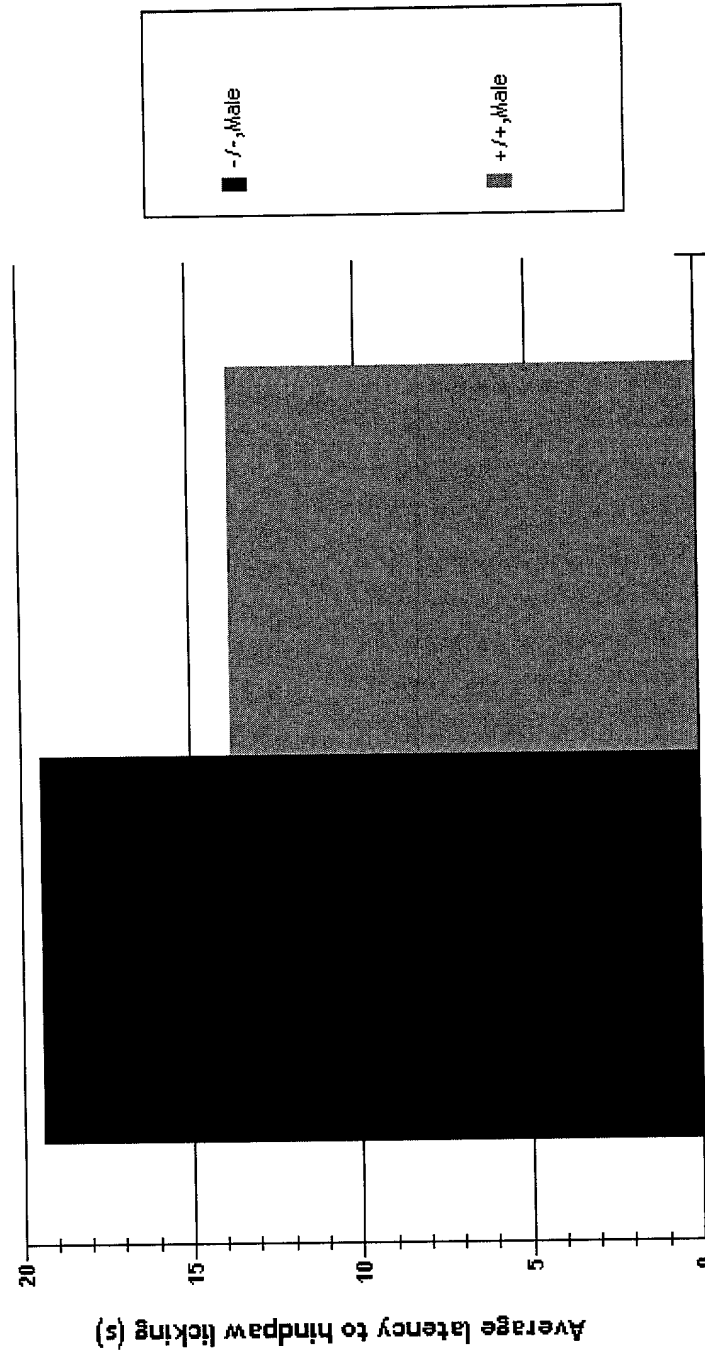


FIGURE 3